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Data Article

Dataset for amiodarone adverse events compared to placebo using data from randomized controlled trials



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A R T I C L E I N F O

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ABSTRACT

The dataset presented here provides a detailed description of the adverse events of amiodarone versus placebo using data from 43 randomized controlled trials. Two authors (M.M., M.R.) independently extracted the data. The dataset also includes baseline patient characteristics, amiodarone loading and maintenance doses, as well as forest plots describing the relative risk (RR) of developing an adverse event related to the pulmonary, thyroid, hepatic, cardiac, skin, gastrointestinal, neurological, and ocular systems. The Mantel-Haenszel random effects model was used to determine the relative risk of adverse events of amiodarone compared to placebo. This dataset is complementary to our article "Meta-analysis Comparing the Relative Risk of Adverse Events for Amiodarone Versus Placebo", which was published in the American Journal of Cardiology [1]. The data can be used to assess certain adverse events and their relation to amiodarone loading and/or maintenance dose.

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Specifications Table

Subject	Cardiology and Cardiovascular Medicine
Specific subject area	A meta-analysis reporting the relative risk of developing adverse events related to amiodarone compared to placebo
T C 1 ·	
Type of data	Tables
	Figures
	Raw data (supplement)
How data were acquired	We searched PubMed, Google Scholar, the Cochrane Central Register for RCTs, and
	ClinicalTrials.gov for studies that evaluated amiodarone use irrespective of indication or
	efficacy of amiodarone therapy
Data format	Raw, Analyzed,
	Filtered
Parameters for data collection	Patients who took amiodarone for prevention and/or treatment of ventricular or atrial
	arrhythmias.
Description of data collection	We searched PubMed, Google Scholar, the Cochrane Central Register for RCTs, and
	ClinicalTrials.gov for studies that evaluated amiodarone use irrespective of indication or
	efficacy of amiodarone therapy. Key search terms used were amiodarone, adverse
	events, side effects, placebo, atrial fibrillation, atrial flutter, ventricular tachycardia,
	arrhythmias, liver, hepatic, skin, thyroid, eye, and lung, and pulmonary. Bibliographies
	of retrieved studies were hand-searched to identify additional relevant studies.
Data source location	Data from randomized controlled trials.
Data accessibility	
5	With the article, and the supplement.
Related research article	Ruzieh M, Moroi MK, Aboujamous NM, Ghahramani M, Naccarelli GV, Mandrola J, Foy AJ.
	Meta-Analysis Comparing the Relative Risk of Adverse Events for Amiodarone Versus
	Placebo. Am J Cardiol. 2019. pii: S0002-9149(19)31046-X. https://doi.org/10.1016/j.
	amjcard.2019.09.008. [Epub ahead of print]

Value of the Data

• This dataset provides detailed description of the adverse events and its relative risk in patients taking amiodarone compared to placebo. This is very important for the medical community as amiodarone is one of commonly used drugs to treat atrial fibrillation.

Medical providers who are prescribing or managing patients taking amiodarone as well as researchers interested in
assessing amiodarone related adverse events.

• Further analysis could be performed to determine how different amiodarone loading and maintenance regimens could affect the development of amiodarone related adverse events.

• Understanding the nature and the rate of amiodarone related adverse events will help physicians develop appropriate screening and monitoring strategies for these events.

1. Data

The raw dataset contains the number of events and number of patient-year for the amiodarone and placebo arm of each study (reads in xlsx format, each organ system in a separate sheet). Patients' characteristics are summarized in Tables 1 and 2. The number and incident rate of events are listed in Table 4. The rate of adverse events in the amiodarone arm for each organ system, and the rate of drug discontinuation compared to placebo are illustrated in Figs. 1–9.

2. Experimental design, materials, and methods

The protocol was developed by three authors (M.M., M.R., A.F.) and revised by all authors.

PubMed, Google Scholar, the Cochrane Central Register for randomized controlled trials, and ClinicalTrials.gov were searched for studies that analyzed the use of amiodarone regardless of indication or efficacy of therapy (latest search was conducted on October 10, 2018). Articles were identified using key search terms: amiodarone, adverse events, side effects, placebo, atrial fibrillation, atrial flutter, ventricular tachycardia, arrhythmias, liver, skin, thyroid, eye, and lung.

Table 1

Baseline patient characteristics. Forty-three randomized control trials [2-20] were studied, and 11,395 patients were included (5792 patients in the amiodarone group, 5603 patients in the placebo group). Average age was 62.0 years for patients receiving amiodarone and 62.3 years for patients receiving placebo. Follow up time ranged from 1 week–6 months for studies with follow up < 12 months. Indications for amiodarone therapy were suppression of atrial and ventricular arrhythmias, and maintenance dose for amiodarone ranged from 200 to 600 mg daily. Raw data for the adverse events is provided in the supplement material.

											Ami	odaron	e arm	Plac	ebo arr	n
First author	Year	Medical condition	Average Ejection fraction		Reason for intervention	Mean follow-up (days)	Average Load Dose (mg/day)	Load (# of days)	Average Maintenance Dose (mg/day)	Maintenance (# of days)	Of	Mean age (yrs)	Male Gender (%)	Of	Mean age (yrs)	Male Gender (%)
Greco	1989	Patients with anterior MI	NA	100%	Reduce mortality and morbidity	Until discharge	10-20 mg/kg	1	N/A	N/A	159	54	85	160	55	87
Hamer	1989	Congestive heart failure	18%	60%	Arrhythmia control, exercise tolerance and ventricular function	180	387	180	200	150	16	70	N/A	14	66	N/A
Hohnloser	1991	Post CABG	NA	100%	Suppression of SVT and ventricular arrhythmias	4	1125	4	N/A	N/A	39	59	76.9	38	59	73.7
Meyer	1993	Stable angina	59%	100%	Limiting angina pectoris	60	400	30	200	50	32	61	N/A	31	58	N/A
Mahmarian	1994	Systolic heart failure and NSVT	24%	49%	Suppression of ventricular arrhythmias	90	422	30	50 or 100	54	32	53.5	77.5	16	51	81
Donovan	1995	Patients with recent- onset AF	NA	48%	Restoration of sinus rhythm	Until discharge	7 mg/kg	1	N/A	N/A	32	56	N/A	32	59	N/A
Galve	1996	Newly diagnosed AF	NA	NA	Rhythm control	15	1200 + 5 mg/kg	1	N/A	N/A	50	60	54	50	61	56
Gentile	1996	Elderly patients with systolic heart failure	<40%	61%	Reduce sudden cardiac death	180	400	30	100	150	24	71	N/A	22	71	N/A
Daoud	1997	Patients undergoing open heart surgery	48%	60%	Prevention of post-op AF	30	200-1000	13 ± 7	N/A	N/A	64	57	68.8	60	67	66.7
Kochiadakis	1998		50%	NA	Restoration of sinus rhythm	1	2100 + 20 mg/kg	1	N/A	N/A	48	63	56	49	65	51
Cotter	1999	Patients with paroxysmal AF	Majority <45%	43%	Restoration of sinus rhythm	30	3000	1	N/A	N/A	50	64.5	48	50	68	38
Kochiadakis	1999	Patients with persistent AF	50%	NA	Restoration of sinus rhythm	30	460 + 20 mg/kg	28	N/A	N/A	33	64	48.5	34	63	47.1
Redle	1999	Patients undergoing CABG	49%	100%	Prevention of post-op AF	10	430	11	N/A	N/A	73	63	83.5	70	64.5	81.4
Bianconi	2000	Patients with AF or AFL	NA	15%	Acute termination of AF or flutter	3–7	5 mg/kg	1	N/A	N/A	54	63	57	54	66	54
Elizari	2000	Patients with acute MI	NA	100%	Reduce morbidity/ mortality	180	900	3	N/A	N/A	542	60.3	80.6	531	60.5	75.1

(continued on next page)

											Amiodarone arm		e arm	Placebo arm		
First author	Year	Medical condition			Reason for intervention	Mean follow-up (days)	Average Load Dose (mg/day)	Load (# of days)	Average Maintenance Dose (mg/day)		Of	Mean age (yrs)	Male Gender (%)	Of	Mean age (yrs)	Male Gender (%)
Lee	2000	Patients undergoing CABG	59%	100%	Prevention of post-op AF	18	150 + 0.4/kg	8	N/A	N/A	74	66	54	76	65	55
Peuhkurinen	2000	Patients with recent- onset AF	63%	21%		1	30 mg/kg	1	N/A	N/A	31	56	81	31	62	65
Vardas	2000	Patients with AF	51%	NA	Restoration of sinus	30	600	28	N/A	N/A	108	64	49.1	100	65	49
Giri	2001	Patients undergoing CABG, valve or combined	43%	98%	Prevention of post-op AF	9	1000	6; 10	N/A	N/A	120	72.7	78	100	72.5	74
Maras	2001	Patients undergoing CABG	44%	100%	Prevention of post-op AF	7	325	8	N/A	N/A	159	58.3	80	156	57.3	76
White	2002	Patients undergoing open heart surgery	43%	35%	Prevention of post-op AF	21-42	1200– 1400	>10; >6	N/A	N/A	120	72.6	78.3	100	72.5	74
Yagdi	2003	Patients undergoing CABG	48%	100%	Prevention of post-op AF	30	400-600 + 10/kg	2; 5; 5	N/A	N/A	77	59.3	80.5	80	61.1	73.7
Auer	2004	Patients undergoing open heart surgery	69%	64%	Prevention of post-op AF	12	667	9	N/A	N/A	63	64	58.7	65	63	58.5
Mitchell	2005	Patients undergoing CABG, valve replacement, repair	58%	75%	Prevention of post-op atrial tachyarrhythmia	13	10 mg/kg	13	N/A	N/A	299	61.3	82.6	302	61.9	81.8
Alcalde	2006	Patients undergoing CABG	53%	100%	Prevention of post-op AF & AFL	10	1800	1–3	N/A	N/A	46	61	63	47	61.1	70.2
Budeus	2006	Patients undergoing CABG	63%	100%	Prevention of post-op AF	0.5	640	7	N/A	N/A	55	64.9	87.3	55	66.7	76.4
Zebis	2007	Patients undergoing CABG	55%	100%	Prevention of post-op AF	30	1200	5	N/A	N/A	125	67	86	125	67	80
Gu	2009	Patients undergoing off-pump CABG	61%	100%	Prevention of post-op AF	21	200 + 70 mg/kg	17	N/A	N/A	100	73.6	75	110	74.2	72
Balla	2011	Newly diagnosed AF	NA	NA	Rhythm control for AF	1	30 mg/kg	1	N/A	N/A	40	58.9	72.5	40	58.6	60
Khitri		AF, AFL	59%	15%	Rhythm control	90	330	30	200	60	108	64.9	73.1	162	62.4	64.9
Riber		Lung cancer surgery	NA	2%	Prevention of post-op AF	30	1200	5	N/A	N/A	122		49	120		47
Darkner	2014	AF patients undergoing RFA	50%	7%	Rhythm control after ablation	180	400	30	200	26	104	62	81	108	61	86

AF: Atrial fibrillation, AFL: Atrial flutter, CABG: Coronary artery bypass graft, IHD: Ischemic heart disease, MI: myocardial infarction, NA: Not available, NSVT: Non-sustained ventricular tachycardia, RFA: Radiofrequency ablation.

M.K. Moroi et al. / Data in brief 28 (2020) 104835

Table 2

Baseline patient characteristics. Forty-three randomized control trials [2–20] were studied, and 11,395 patients were included (5792 patients in the amiodarone group, 5603 patients in the placebo group). Average age was 62.0 years for patients receiving amiodarone and 62.3 years for patients receiving placebo. Follow up time ranged from 12–54 months in studies with follow up \geq 12 months. Indications for amiodarone therapy were suppression of atrial and ventricular arrhythmias, and maintenance dose for amiodarone ranged from 200 to 600 mg daily. Raw data for the adverse events is provided in the supplement material.

											Amioc	larone	arm	Placel	bo arm	
First author	Year	Medical condition	Average ejection fraction		Reason for intervention	Mean follow-up (months)		Load (day)	Average maintenance dose (mg)	Average maintenance (days)		Mean age (year)	Gender		f Mean age (year)	Gender
Nicklas	1991	Heart failure and frequent ventricular ectopy	20%	52%	Reduce sudden cardiac death	12	400	28	200	215	49	56	83.7	52	59	86.5
Ceremuzynski	1992	Post MI	Majority > 40%	100%	Reduce mortality and ventricular arrhythmias	12	800	7	200-400	306	305	59.4	71.1	308	58.6	68.2
Singh[36]	1995	Patients with CHF and vent arrhythmia	<40%	71%	Improve mortality	45	800	14	328	1246	336	65	99.1	338	66.1	98.8
Cairns	1997	Survivors of MI with frequent or repetitive PVCs	NA	100%	Resuscitated ventricular fibrillation or arrhythmic death	21.5	20/kg	14	200-400	365–730	606	64	82.5	596	64	82
Julian	1997	Survivors of MI and $EF \leq 40\%$	30%	35%	All-cause mortality	21	450	112	200	253–618	743	59.6	83.8	743	60.2	84.9
Singh	1997	Patients with CHF, COPD and patients undergoing surgery	25– 30%	NA	Evaluate pulmonary toxicity	45	800	14	300-400	365-1620	269	65	N/A	250	65.8	N/A
Kochiadakis	2000	Paroxysmal AF	55%	NA	Rhythm control	22	12.5/kg	14	200	720	65	63.2	52.3	60	62.8	51.7
Channer		Persistent AF undergoing DCCV	59%	30%	Rhythm control	54	800	14	200	364	61	66	77	38	68	79
Vora	2004	Patients with chronic rheumatic AF	56%	NA	Rhythm or rate control	12	600	10	200	355	48	39.5	47.9	48	38	45.8
Singh	2005	Persistent AF	50%	25%	Rhythm control	12-54	700	28	200-300	>365	267	67.1	99.3	137	67.7	99.3
Vilvanathan	2016	AF in patients post BMV	58%	1%	Rhythm control for AF	12	500	28	200	365	44	38.8	20.5	45	37.62	34.1

AF: Atrial fibrillation, BMV: balloon mitral valvuloplasty, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, DCCV: direct current cardioversion, EF: Ejection fraction, IHD: Ischemic heart disease, MI: myocardial infarction, NA: Not available, PVC: premature ventricular contraction.

Table 3Risk of bias. Majority of trials included in this analysis were double blinded, decreasing both performance and detection biases.

Bias	Study	Judgement	Support for Judgement
Random sequence generation (selection bias)			
	Greco 1989	Low risk	Randomized on a consecutive basis
	Hamer 1989	Unknown	Unclear method of randomization
	Hohnloser 1991	Unknown	Unclear method of randomization
	Nicklas 1991	Unknown	Unclear method of randomization
	Ceremuzynski 1992	Unknown	Unclear method of randomization
	Meyer 1993	Unknown	Unclear method of randomization
	Mahmarian 1994	Unknown	Unclear method of randomization
	Donovan 1995	Unknown	Unclear method of randomization
	Singh 1995	Unknown	Unclear method of randomization
	Galve 1996	Low risk	Randomized on a consecutive basis
	Gentile 1996	Unknown	Unclear method of randomization
	Cairns 1997	Low risk	Computer generated randomization
	Daoud 1997	Unknown	Unclear method of randomization
	Julian 1997	Low risk	Computer generated randomization
	Singh 1997	Unknown	Unclear method of randomization
	Kochiadakis 1998	Low risk	Randomized on a consecutive basis
	Cotter 1999	Unknown	Unclear method of randomization
	Kochiadakis 1999	Low risk	Randomized on a consecutive basis
	Redle 1999	Unknown	Unclear method of randomization
	Bianconi 2000	Unknown	Unclear method of randomization
	Elizari 2000	Low risk	Random numeric sequence
	Kochiadakis 2000	Unknown	Unclear method of randomization
	Lee 2000	Unknown	Unclear method of randomization
	Peuhkurinen 2000	Unknown	Unclear method of randomization
	Vardas 2000	Unknown	Unclear method of randomization
	Giri 2001	Unknown	Unclear method of randomization
	Maras 2001	Unknown	Unclear method of randomization
	White 2002	Low risk	Computer generated randomization
	Yagdi 2003	Unknown	Unclear method of randomization
	Auer 2004	Low risk	Randomization table
	Channer 2004	Low risk	Random numeric sequence
	Vora 2004	Unknown	Unclear method of randomization
	Mitchell 2005	Low risk	Computer generated randomization
	Singh 2005	Low risk	Permuted-block randomization

	Alcalde 2006	Unknown	Unclear method of randomization
	Budeus 2006	Low risk	Computer generated randomization
	Zebis 2007	Low risk	Computer generated randomization
	Gu 2009	Low risk	Computer generated randomization
	Balla 2011	Low risk	Number assignment by envelope
	Darkner 2012	Low risk	Randomization code
	Khitri 2012	Unknown	Unclear method of randomization
	Riber 2013	Low risk	Computer generated randomization
	Vilvanathan 2016	Unknown	Unclear method of randomization
Allocation			
concealment			
(selection bias)			
	Greco 1989	High risk	Randomized on a consecutive basis
	Hamer 1989	Unknown	Unclear method of randomization
	Hohnloser 1991	Unknown	Unclear method of randomization
	Nicklas 1991	Unknown	Unclear method of randomization
	Ceremuzynski 1992	Unknown	Unclear method of randomization
	Meyer 1993	Unknown	Unclear method of randomization
	Mahmarian 1994	Unknown	Unclear method of randomization
	Donovan 1995	Unknown	Unclear method of randomization
	Singh 1995	Unknown	Unclear method of randomization
	Galve 1996	High risk	Randomized on a consecutive basis
	Gentile 1996	Unknown	Unclear method of randomization
	Cairns 1997	Low risk	Computer generated randomization
	Daoud 1997	Unknown	Unclear method of randomization
	Julian 1997	Low risk	Computer generated randomization
	Singh 1997	Unknown	Unclear method of randomization
	Kochiadakis 1998	High risk	Randomized on a consecutive basis
	Cotter 1999	Unknown	Unclear method of randomization
	Kochiadakis 1999	High risk	Randomized on a consecutive basis
	Redle 1999	Unknown	Unclear method of randomization
	Bianconi 2000	Unknown	Unclear method of randomization
	Elizari 2000	Low risk	Random numeric sequence
	Kochiadakis 2000	Unknown	Unclear method of randomization
	Lee 2000	Unknown	Unclear method of randomization
	Peuhkurinen 2000	Unknown	Unclear method of randomization
	Vardas 2000	Unknown	Unclear method of randomization

	Giri 2001	Unknown	Unclear method of randomization
	Maras 2001	Unknown	Unclear method of randomization
	White 2002	Low risk	Computer generated randomization
	Yagdi 2003	Unknown	Unclear method of randomization
	Auer 2004	Low risk	Randomization table
	Channer 2004	Low risk	Random numeric sequence
	Vora 2004	Unknown	Unclear method of randomization
	Mitchell 2005	Low risk	Computer generated randomization
	Singh 2005	Low risk	Permuted-block randomization
	Alcalde 2006	Unknown	Unclear method of randomization
	Budeus 2006	Low risk	Computer generated randomization
	Zebis 2007	Low risk	Computer generated randomization
	Gu 2009	Low risk	Computer generated randomization
	Balla 2011	Low risk	Number assignment by envelope
	Darkner 2012	Low risk	Randomization code
	Khitri 2012	Unknown	Unclear method of randomization
	Riber 2013	Low risk	Computer generated randomization
	Vilvanathan 2016	Unknown	Unclear method of randomization
Blinding of			
participants and			
personnel			
(performance bias)			
	Greco 1989	High risk	Participants were not blinded
	Hamer 1989	Low risk	Double blinded design
	Hohnloser 1991	High risk	Participants were not blinded
	Nicklas 1991	Low risk	Double blinded design
	Ceremuzynski 1992	Low risk	Double blinded design
	Meyer 1993	Low risk	Double blinded design
	Mahmarian 1994	low risk	Double blinded design
	Donovan 1995	Low risk	Double blinded design
	Singh 1995	Low risk	Double blinded design
	Galve 1996	Unknown	Blinding not specified
	Gentile 1996	Low risk	Double blinded design
	Cairns 1997	Low risk	Double blinded design
	Daoud 1997	Low risk	Double blinded design
	Julian 1997	Low risk	Double blinded design
	Singh 1997	Low risk	Double blinded design

	Kochiadakis 1998	Low risk	Double blind design
	Cotter 1999	Unknown	Blinding not specified
	Kochiadakis 1999	Low risk	Participants were blinded
	Redle 1999	Low risk	Double blinded design
	Bianconi 2000	Low risk	Double blinded design
	Elizari 2000	Low risk	Double blinded design
	Kochiadakis 2000	Low risk	Participants were blinded
	Lee 2000	Low risk	Double blinded design
	Peuhkurinen 2000	Unknown	Blinding not specified
	Vardas 2000	Unknown	Blinding not specified
	Giri 2001	Low risk	Double blinded design
	Maras 2001	Low risk	Double blinded design
	White 2002	Low risk	Double blinded design
	Yagdi 2003	Low risk	Double blinded design
	Auer 2004	Low risk	Double blinded design
	Channer 2004	Low risk	Double blinded design
	Vora 2004	Low risk	Double blinded design
	Mitchell 2005	Low risk	Double blinded design
	Singh 2005	Low risk	Double blinded design
	Alcalde 2006	Low risk	Double blinded design
	Budeus 2006	Low risk	Double blinded design
	Zebis 2007	Low risk	Double blinded design
	Gu 2009	Low risk	Double blinded design
	Balla 2011	Low risk	Participants were blinded
	Darkner 2012	Low risk	Double blinded design
	Khitri 2012	Unknown	Blinding not specified
	Riber 2013	Low risk	Double blinded design
	Vilvanathan 2016	Unknown	Blinding not specified
Blinding of			
outcome			
assessment			
(detection bias)			
	Greco 1989	High risk	Outcome assessors were not blinded
	Hamer 1989	Low risk	Double blinded design
	Hohnloser 1991	High risk	Outcome assessors were not blinded
	Nicklas 1991	Low risk	Double blinded design
	Ceremuzynski 1992	Low risk	Double blinded design

Meyer 1993	Low risk	Double blinded design
Mahmarian 1994	low risk	Double blinded design
Donovan 1995	Low risk	Double blinded design
Singh 1995	Low risk	Double blinded design
Galve 1996	Unknown	Blinding not specified
Gentile 1996	Low risk	Double blinded design
Cairns 1997	Low risk	Double blinded design
Daoud 1997	Low risk	Double blinded design
Julian 1997	Low risk	Double blinded design
Singh 1997	Low risk	Double blinded design
Kochiadakis 1998	Low risk	Double blind design
Cotter 1999	Unknown	Blinding not specified
Kochiadakis 1999	High risk	Outcome assessors were not blinded
Redle 1999	Low risk	Double blinded design
Bianconi 2000	Low risk	Double blinded design
Elizari 2000	Low risk	Double blinded design
Kochiadakis 2000	High risk	Outcome assessors were not blinded
Lee 2000	Low risk	Double blinded design
Peuhkurinen 2000	Unknown	Blinding not specified
Vardas 2000	Unknown	Blinding not specified
Giri 2001	Low risk	Double blinded design
Maras 2001	Low risk	Double blinded design
White 2002	Low risk	Double blinded design
Yagdi 2003	Low risk	Double blinded design
Auer 2004	Low risk	Double blinded design
Channer 2004	Low risk	Double blinded design
Vora 2004	Low risk	Double blinded design
Mitchell 2005	Low risk	Double blinded design
Singh 2005	Low risk	Double blinded design
Alcalde 2006	Low risk	Double blinded design
Budeus 2006	Low risk	Double blinded design
Zebis 2007	Low risk	Double blinded design
Gu 2009	Low risk	Double blinded design
Balla 2011	High risk	Outcome assessors were not blinded
Darkner 2012	Low risk	Double blinded design
Khitri 2012	Unknown	Blinding not specified
Riber 2013	Low risk	Double blinded design

	Vilvanathan 2016	Unknown	Blinding not specified
Incomplete			
outcome data			
addressed (attrition			
bias)			
	Greco 1989	Low risk	No significant attrition
	Hamer 1989	Low risk	No significant attrition
	Hohnloser 1991	Low risk	No significant attrition
	Nicklas 1991	Low risk	No significant attrition
	Ceremuzynski 1992	Low risk	No significant attrition
	Meyer 1993	Low risk	No significant attrition
	Mahmarian 1994	Low risk	No significant attrition
	Donovan 1995	Low risk	No significant attrition
	Singh 1995	Low risk	No significant attrition
	Galve 1996	Low risk	No significant attrition
	Gentile 1996	Low risk	No significant attrition
	Cairns 1997	Low risk	No significant attrition
	Daoud 1997	Low risk	No significant attrition
	Julian 1997	Low risk	No significant attrition
	Singh 1997	Low risk	No significant attrition
	Kochiadakis 1998	Low risk	No significant attrition
	Cotter 1999	Low risk	No significant attrition
	Kochiadakis 1999	Low risk	No significant attrition
	Redle 1999	Low risk	No significant attrition
	Bianconi 2000	Low risk	No significant attrition
	Elizari 2000	High risk	Early study termination
	Kochiadakis 2000	Low risk	No significant attrition
	Lee 2000	Low risk	No significant attrition
	Peuhkurinen 2000	Low risk	No significant attrition
	Vardas 2000	Low risk	No significant attrition
	Giri 2001	Low risk	No significant attrition
	Maras 2001	Low risk	No significant attrition
	White 2002	Low risk	No significant attrition
	Yagdi 2003	Low risk	No significant attrition
	Auer 2004	Low risk	No significant attrition
	Channer 2004	Low risk	No significant attrition
	Vora 2004	Low risk	No significant attrition

	Mitchell 2005	Low risk	
	Singh 2005	Low risk	No significant attrition
	Alcalde 2006	Low risk	No significant attrition
	Budeus 2006	Low risk	No significant attrition
	Zebis 2007	Low risk	No significant attrition
	Gu 2009	Low risk	No significant attrition
	Balla 2011	Low risk	No significant attrition
	Darkner 2012	Low risk	No significant attrition
	Khitri 2012	Low risk	No significant attrition
	Riber 2013	Low risk	No significant attrition
	Vilvanathan 2016	Low risk	No significant attrition
Selective reporting (reporting bias)			
	Greco 1989	Low risk	
	Hamer 1989	Low risk	
	Hohnloser 1991	Low risk	
	Nicklas 1991	Low risk	
	Ceremuzynski 1992	Low risk	
	Meyer 1993	Low risk	
	Mahmarian 1994	Low risk	
	Donovan 1995	Low risk	
	Singh 1995	Low risk	
	Galve 1996	Low risk	
	Gentile 1996	Low risk	
	Cairns 1997	Low risk	
	Daoud 1997	Low risk	
	Julian 1997	Low risk	
	Singh 1997	Low risk	
	Kochiadakis 1998	Low risk	
	Cotter 1999	Low risk	
	Kochiadakis 1999	Low risk	
	Redle 1999	Low risk	
	Bianconi 2000	Low risk	
	Elizari 2000	Low risk	
	Kochiadakis 2000	Low risk	
	Lee 2000	Low risk	

]	Peuhkurinen 2000	Low risk	
	Vardas 2000	Low risk	
(Giri 2001	Low risk	
]	Maras 2001	Low risk	
1	White 2002	Low risk	
	Yagdi 2003	Low risk	
	Auer 2004	Low risk	
(Channer 2004	Low risk	
,	Vora 2004	Low risk	
]	Mitchell 2005	Low risk	
1	Singh 2005	Low risk	
	Alcalde 2006	Low risk	
]	Budeus 2006	Low risk	
	Zebis 2007	Low risk	
	Gu 2009	Low risk	
]	Balla 2011	Low risk	
]	Darkner 2012	Low risk	
]	Khitri 2012	Low risk	
]	Riber 2013	Low risk	
,	Vilvanathan 2016	Low risk	

Highlighted are studies with follow up ≥ 12 months.

References of all identified studies were also hand-searched for inclusion to identify additional relevant studies [1].

All articles were then independently reviewed for inclusion in this analysis by two authors (M.M., M.R.). Inclusion criteria were: 1) randomized control trial, 2) documentation of adverse events and drug discontinuation due to adverse events, 3) presence of placebo arm. Data on sample size, follow up, and outcomes were then extracted. Discrepancies were discussed and resolved by consensus.

Primary outcomes of this analysis were pulmonary, hepatic, thyroid, ocular, cardiac, skin, and neurological adverse events, as well as drug discontinuation related to adverse side effects. Specific adverse events within each organ system were also reported. All adverse events were presented as incident rate per 10,000 person-years.

The Cochrane Risk of Bias table and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) System were utilized to determine risk of bias and quality of the outcomes in all trials incorporated into this analysis (Table 3).

RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration; Copenhagen, Denmark) was used to conduct the primary analysis. Relative risk (RR) was determined for all studies using the Mantel-Haenszel random effects model with 95% confidence interval (CI) to establish the likelihood of adverse events. A secondary analysis was also performed to determine the RR for studies with follow up < 12 months and \geq 12 months. Sensitivity analyses were used to show the robustness of the results. Heterogeneity was calculated using I², a value which represents the percentage of variability in the effect risk estimate among studies due to heterogeneity rather than chance (I² <25% considered as low, I² between 25% and 75% as intermediate, I² >75% considered as high). Begg's funnel plots method was utilized to investigate potential publication bias. A p-value of <0.05 was used to determine statistical significance.

Table 4

Number of events, incident rate, and relative risk of specific adverse events for amiodarone compared to placebo.

organ system		Follow up \geq 12 m events (events/10,			All, No. of events (events/10,000 patient year)			
		Amiodarone arm	Placebo	RR (95% CI), P value	Amiodarone arm	Placebo	RR (95% CI), P value	
Pulmonary adverse events	Pulmonary fibrosis	8 (13)	6(11)		8 (12)	6(11)		
	Cough	0 (0)	0(0)		1 (1)	0(0)		
	Lung infiltrates	0(0)	0(0)		1(1)	0(0)		
	Unspecified	77 (124)	40 (70)		77 (115)	40 (65)		
	Total	85 (136)	46 (81)	1.74 (1.21–2.50), 0.003	87 (129)	46 (74)	1.77 (1.24–2.52), 0.002	
Thyroid adverse events	Clinical hyperthyroidism	19 (36)	4 (8)		19 (33)	5 (9)		
	Clinical hypothyroidism	27 (52)	0(0)		27 (47)	0(0)		
	Subclinical change in TFT	13 (25)	3 (6)		40 (70)	8 (15)		
	Unspecified	24 (46)	5(11)		29 (51)	9 (17)		
	Total	83 (159)	12 (25)	5.32 (2.99-9.44), < 0.001	115 (201)	22 (42)	4.44 (2.87–6.89), < 0.00	
Liver adverse events	Liver failure	0(0)	0(0)		0(0)	0(0)		
	Elevated liver enzymes	8 (15)	3 (6)		10 (18)	5 (10)		
	Unspecified	21 (40)	8 (17)		21 (37)	8 (15)		
	Total	29 (56)	11 (23)	2.42 (1.23-4.74), 0.01	31 (54)	13 (25)	2.27 (1.20-4.29), 0.01	
Cardiac adverse events	Bradyarrhythmias	100 (192)	34 (72)		267 (468)	128 (244)		
	Hypotension	0(0)	0(0)		98 (172)	65 (124)		
	Long QT	5 (10)	0(0)		18 (32)	0(0)		
	Torsade de pointes	0(0)	0(0)		0(0)	0(0)		
	Worsening heart failure	1 (2)	1 (2)		5 (9)	5 (10)		
	Unspecified conduction	0(0)	0(0)		46 (81)	32 (61)		
	disease							
	Unspecified	0(0)	0(0)		6(11)	6(11)		
	Total	106 (203)	35 (74)	2.76 (1.91–3.98), < 0.001	440 (771)	236 (450)	1.94 (1.39-2.71) < 0.001	
Skin adverse events	Blue/gray discoloration of skin	2 (4)	3 (6)	,	2 (4)	3 (6)		
	Photosensitivity	1 (2)	0(0)		11 (19)	0(0)		
	Unspecified rash/flushing	21 (40)	9 (19)		33 (58)	9(17)		
	Total	24 (46)	12 (25)	1.51 (0.73–3.11), 0.26	46 (81)	12 (23)	1.99 (1.04–3.78), 0.04	
GI adverse events	Dyspepsia/nausea/ vomiting	20 (38)	16 (34)		122 (214)	74 (141)		
	Diarrhea	0(0)	0(0)		8 (14)	4(8)		
	Unspecified	35 (67)	25 (53)		62 (109)	33 (63)		
	Total	55 (105)	41 (86)	1.36 (0.91–2.04), 0.14	192 (109) 192 (336)	111 (212)	1.63 (1.18–2.24), 0.003	

2.19), < 0.00
10.36), 0.08
2.65), < 0.00

	Amioda	rone	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
Hamer 1989	0	8	0	7		Not estimable	1989	
Greco 1989	0	7	0	7		Not estimable	1989	
Nicklas 1991	0	49	0	52		Not estimable	1991	
Ceremuzynski 1992	1	305	0	308	1.2%	3.03 [0.12, 74.07]	1992	
Meyer 1993	0	5	0	5		Not estimable	1993	
Mahmarian 1994	0	8	0	4		Not estimable	1994	
Singh 1995	10	1260	4	1268	9.4%	2.52 [0.79, 8.00]	1995	
Donovan 1995	0	1	0	1		Not estimable	1995	
Galve 1996	0	2	0	2		Not estimable	1996	
Gentile 1996	0	12	0	11		Not estimable	1996	
Cairns 1997	23	1086	7	1068	17.8%	3.23 [1.39, 7.50]	1997	_ _
Julian 1997	39	1300	30	1300	57.3%	1.30 [0.81, 2.08]	1997	
Singh 1997	10	1009	4	938	9.5%	2.32 [0.73, 7.38]	1997	
Daoud 1997	0	5	0	5		Not estimable	1997	
Kochiadakis 1998	0	0	0	0		Not estimable	1998	
Kochiadakis 1999	0	3	0	3		Not estimable	1999	
Redle 1999	0	2	0	2		Not estimable	1999	
Cotter 1999	0	4	0	4		Not estimable	1999	
Lee 2000	0	4	0	4		Not estimable	2000	
Kochiadakis 2000	0	119	0	110		Not estimable	2000	
Peuhkurinen 2000	0	0	0	0		Not estimable	2000	
Vardas 2000	0	9	0	8		Not estimable		
Bianconi 2000	0	1	0	1		Not estimable	2000	
Elizari 2000	1	271	0	266	1.2%	2.94 [0.12, 71.97]		
Maras 2001	0	3	0	3		Not estimable		
Giri 2001	0	3	0	3		Not estimable		
White 2002	0	15	0	13		Not estimable		
Yaqdi 2003	0	6	0	7		Not estimable		
Channer 2004	0	275	0	171		Not estimable		
Auer 2004	0	2	0	2		Not estimable		
Vora 2004	0	48	0	48		Not estimable		
Singh 2005	2	734	1	377	2.2%	1.03 [0.09, 11.29]		
Mitchell 2005	1	12	0	12	1.3%	3.00 [0.13, 67.06]		
Alcalde 2006	ō	1	0	1	210/0	Not estimable		
Budeus 2006	Ő	2	Ő	2		Not estimable		
Zebis 2007	0	10	0	10		Not estimable		
Gu 2009	Ő	5	Ő	6		Not estimable		
Balla 2011	õ	0	ő	ŏ		Not estimable		
Khitri 2012	õ	27	Ő	41		Not estimable		
Darkner 2012	Ő	52	Ő	54		Not estimable		
Riber 2013	ŏ	10	0	10		Not estimable		
Vilvanathan 2016	0	44	0	45		Not estimable		
Total (95% CI)		6719		6179	100.0%	1.77 [1.24, 2.52]		◆
Total events	87		46					
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 4.7$	3, df = 7	P = 0	.69); $I^2 =$	0%		
Test for overall effect:						27429425		0.01 0.1 1 10 100

Fig. 1. Pulmonary adverse events. "Total" represents total events per 10,000 person-years. The incident rate of pulmonary adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (129 vs 74; RR: 1.77; 95% CI [1.24–2.52], $P = 0.002, 1^2; 0\%$).

	Amioda	rone	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Greco 1989	0	7	0	7		Not estimable	1989	
Hamer 1989	0	8	0	7		Not estimable	1989	
Nicklas 1991	0	49	0	52		Not estimable	1991	
Ceremuzynski 1992	11	305	1	308	4.6%	11.11 [1.44, 85.51]	1992	· · · · · · · · · · · · · · · · · · ·
Meyer 1993	0	5	0	5		Not estimable		
Mahmarian 1994	0	8	0	4		Not estimable		
Singh 1995	4	1260	2	1268	6.7%	2.01 [0.37, 10.97]		
Donovan 1995	0	1	0	1		Not estimable		
Galve 1996	0	2	0	2		Not estimable		
Gentile 1996	0	12	0	11		Not estimable		
Cairns 1997	24	1086	5	1068	20.9%	4.72 [1.81, 12.33]		
Julian 1997	23	1300	4	1300	17.1%	5.75 [1.99, 16.58]		
Daoud 1997	0	5	0	5	,.	Not estimable		
Kochiadakis 1998	Ő	ő	0	Ő		Not estimable		
Cotter 1999	0	4	Ő	4		Not estimable		
Kochiadakis 1999	0	3	Ő	3		Not estimable		
Redle 1999	0	2	0 0	2		Not estimable		
Kochiadakis 2000	12	119	0	110	2.4%	23.13 [1.39, 385.99]		
Bianconi 2000	0	115	0	110	2.4/0	Not estimable		
Elizari 2000	2	271	2	266	5.0%	0.98 [0.14, 6.92]		
Lee 2000	0	4	0	200	5.0%	Not estimable		
Peuhkurinen 2000	0	0	0	4		Not estimable		
Vardas 2000	0	9	0	8		Not estimable		
Giri 2001	0	3	0	3		Not estimable		
Maras 2001	0	3	0	3		Not estimable		
White 2002	0	15	0	13		Not estimable		
	0	15	0	7				
Yagdi 2003 Vora 2004	2	48	0	48	2.1%	Not estimable		
Channer 2004	4	275	0	171	2.1%	5.00 [0.25, 101.48]		
	4	275	0	2	2.3%	5.61 [0.30, 103.53]		,
Auer 2004	-		-	377		Not estimable		
Singh 2005	0	734	0			Not estimable		
Mitchell 2005	0	12	0	12		Not estimable		
Alcalde 2006	0	1	0	1		Not estimable		
Budeus 2006	0	2	0	2		Not estimable		
Zebis 2007	0	10	0	10		Not estimable		
Gu 2009	0	5	0	6		Not estimable		
Balla 2011	0	0	0	0		Not estimable		
Darkner 2012	27	52	6	54	30.1%	4.67 [2.10, 10.38]		
Khitri 2012	3	27	2	41	6.5%	2.28 [0.41, 12.75]		
Riber 2013	0	10	0	10	141 - 2017 20	Not estimable		
Vilvanathan 2016	3	44	0	45	2.2%	7.16 [0.38, 134.62]	2016	
Total (95% CI)		5710		5241	100.0%	4.44 [2.87, 6.89]		•
Total events	115		22					
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 6.4$	1, df = 1	LO (P =	0.78); I ² :	= 0%		0.01 0.1 1 10 100
Test for overall effect:								0.01 0.1 1 10 100 Placebo Amiodarone

Fig. 2. Thyroid adverse events. "Total" represents total events per 10,000 person-years. The incident rate of thyroid adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (201 vs 42; RR: 4.44; 95% CI [2.87–6.89], P < 0.001, 1^2 : 0%).

	Amioda		Place			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
Greco 1989	0	7	0	7		Not estimable	1989	
lamer 1989	0	8	0	7		Not estimable	1989	
Nicklas 1991	1	49	1	52	5.3%	1.06 [0.07, 16.50]	1991	
Ceremuzynski 1992	0	305	0	308		Not estimable	1992	
Meyer 1993	0	5	0	5		Not estimable	1993	
Mahmarian 1994	0	8	0	4		Not estimable	1994	
Donovan 1995	0	1	0	1		Not estimable	1995	
Singh 1995	4	1260	2	1268	14.0%	2.01 [0.37, 10.97]	1995	
Galve 1996	0	2	0	2		Not estimable	1996	
Gentile 1996	0	12	0	11		Not estimable	1996	
Daoud 1997	0	5	0	5		Not estimable	1997	
airns 1997	6	1086	2	1068	15.8%	2.95 [0.60, 14.58]	1997	
ulian 1997	15	1300	6	1300	45.2%	2.50 [0.97, 6.42]		⊢_
ochiadakis 1998	0	0	Ő	0		Not estimable		
Cotter 1999	Ő	4	Ő	4		Not estimable		
ochiadakis 1999	Ő	3	Ő	3		Not estimable		
edle 1999	0	2	0	2		Not estimable		
ianconi 2000	0	1	0	1		Not estimable		
lizari 2000	0	271	1	266	3.9%	0.33 [0.01, 8.00]		
ee 2000	0	4	0	4	5.570	Not estimable		
euhkurinen 2000	Ő	0	0	0		Not estimable		
ochiadakis 2000	0	119	0	110		Not estimable		
ardas 2000	0	9	0	8		Not estimable		
Giri 2001	0	3	0	3		Not estimable		
Maras 2001	0	3	0	3		Not estimable		
White 2002	0	15	0	13		Not estimable		
	0	6	0	7		Not estimable		
'agdi 2003	0	2	0	2		Not estimable		
uer 2004	-	48	-					
ora 2004	0		0	48	2.00/	Not estimable		
hanner 2004	1	275	0	171	3.9%	1.87 [0.08, 45.63]		
litchell 2005	0	12	0	12		Not estimable		
ingh 2005	0	734	0	377		Not estimable		
udeus 2006	0	2	0	2		Not estimable		
Icalde 2006	0	1	0	1		Not estimable		
ebis 2007	0	10	0	10		Not estimable		
iu 2009	0	5	0	6		Not estimable		
alla 2011	0	0	0	0		Not estimable		
arkner 2012	0	52	0	54		Not estimable		
hitri 2012	2	27	1	41	7.3%	3.04 [0.29, 31.87]		
liber 2013	0	10	0	10		Not estimable		
/ilvanathan 2016	2	44	0	45	4.5%	5.11 [0.25, 103.53]	2016	
Fotal (95% CI)		5710		5241	100.0%	2.27 [1.20, 4.29]		•
Fotal events	31		13					
leterogeneity: Tau ² =	0.00 [.] Ch	$i^2 = 2.2$	2. df = 7	P = 0	.95); $I^2 =$	0%		0.01 0.1 1 10 10

Fig. 3. Liver adverse events. "Total represents total events per 10,000 person-years. Liver adverse events were rare, but the rate of liver adverse events per 10,000 person-years was still higher in the amiodarone group versus placebo (54 vs 25; RR: 2.27; 95% CI [1.20–4.29], P = 0.01, l^2 : 0%).

Study on Cubanaun	Amioda		Place		Walakt	Risk Ratio	Veen	Risk Ratio
Study or Subgroup	Events				weight	M-H, Random, 95% CI		M-H, Random, 95% Cl
Hamer 1989	0 25	8 7	0 4	7		Not estimable		
Greco 1989						Not estimable		
Hohnloser 1991	7	0	5	0		Not estimable		
Nicklas 1991	2	49	0	52	1.2%	5.30 [0.26, 107.70]		
Ceremuzynski 1992	69	305	23	308	21.0%	3.03 [1.94, 4.73]		
Meyer 1993	0	5	0	5		Not estimable		
Mahmarian 1994	0	8	0	4	-	Not estimable		
Singh 1995	6	1260	5	1268	6.4%	1.21 [0.37, 3.95]		
Donovan 1995	5	1	8	1		Not estimable		
Galve 1996	4	2	5	2		Not estimable		
Gentile 1996	0	12	0	11		Not estimable		
ulian 1997	10	1300	1	1300	2.5%	10.00 [1.28, 78.01]	1997	
Cairns 1997	8	1086	5	1068	7.1%	1.57 [0.52, 4.79]	1997	
Daoud 1997	0	5	0	5		Not estimable	1997	
(ochiadakis 1998	0	0	0	0		Not estimable	1998	
Kochiadakis 1999	5	3	0	3		Not estimable	1999	
Redle 1999	0	2	2	2	1.6%	0.20 [0.02, 2.64]	1999	
Cotter 1999	5	4	2	4		Not estimable	1999	
ee 2000	2	4	0	4	1.4%	5.00 [0.31, 79.94]	2000	· · · · · ·
euhkurinen 2000	1	0	1	0		Not estimable	2000	
/ardas 2000	12	9	0	8		Not estimable	2000	
ochiadakis 2000	2	119	0	110	1.2%	4.63 [0.22, 95.28]		
Bianconi 2000	1	1	0	1	1.7%	3.00 [0.24, 37.67]		
Elizari 2000	105	271	70	266	28.0%	1.47 [1.15, 1.89]		-
Maras 2001	13	3	9	3		Not estimable		
Giri 2001	55	3	38	3		Not estimable		
White 2002	44	15	34	13		Not estimable		
aqdi 2003	4	6	2	7	5.5%	2.33 [0.64, 8.57]		
/ora 2004	2	48	1	48	1.9%	2.00 [0.19, 21.33]		
Channer 2004	3	275	0	171	1.2%	4.36 [0.23, 83.94]		
Auer 2004	5	2/5	4	2	1.2/0	Not estimable		
Auer 2004 Aitchell 2005	21	12	4	12		Not estimable		
Singh 2005	21	734	0	377		Not estimable		
Alcalde 2006	0	/34	0	377		Not estimable		
Sudeus 2006	3	2	1	2		Not estimable		
ebis 2005	3	10	1	10	2.1%			
	2	5				2.00 [0.21, 18.69]		
Gu 2009	-		1	6	1.7%	1.20 [0.10, 14.69]		
Salla 2011	0	0	0	0	1 201	Not estimable		
Chitri 2012	7	27	0	41	1.3%	22.50 [1.34, 378.42]		
Darkner 2012	2	52	2	54	2.8%	1.04 [0.15, 7.10]		
Riber 2013	5	10	5	10	10.1%	1.00 [0.42, 2.40]		
/ilvanathan 2016	4	44	0	45	1.3%	9.20 [0.51, 165.99]	2016	
Total (95% CI)		5710		5241	100.0%	1.94 [1.39, 2.71]		•
Fotal events	440		236					
leterogeneity: Tau ² =	0.09; Ch	$i^2 = 23.$	31, df =	18 (P =	= 0.18); I ²	= 23%		0.01 0.1 1 10 10
est for overall effect				ANON 1050				0.01 0.1 1 10 1 Placebo Amiodarone

Fig. 4. Cardiac adverse events. "Total" represents total events per 10,000 person-years. Cardiac adverse events were the most commonly reported adverse events for both groups. The incident rate of cardiac adverse events per 10,000 person-years was higher in patients receiving amiodarone versus placebo (771 vs 450; RR: 1.94; 95% CI [1.39–2.71], P = 0.0001, I²: 23%).

	Amioda	rone	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
Greco 1989	9	7	0	7		Not estimable	1989	
Hamer 1989	2	8	0	7	5.0%	4.44 [0.25, 79.42]	1989	
Nicklas 1991	1	49	1	52	5.5%	1.06 [0.07, 16.50]	1991	
Ceremuzynski 1992	1	305	1	308	5.4%	1.01 [0.06, 16.07]	1992	
Meyer 1993	0	5	0	5		Not estimable	1993	
Mahmarian 1994	2	8	0	4	5.2%	2.78 [0.16, 47.20]	1994	
Singh 1995	1	1260	2	1268	7.2%	0.50 [0.05, 5.54]	1995	
Donovan 1995	0	1	0	1		Not estimable	1995	
Galve 1996	0	2	0	2		Not estimable	1996	
Gentile 1996	0	12	0	11		Not estimable	1996	
Cairns 1997	12	1086	8	1068	52.3%	1.48 [0.61, 3.59]	1997	- +
Daoud 1997	0	5	0	5		Not estimable		_
Iulian 1997	8	1300	0	1300	5.1%	17.00 [0.98, 294.22]		
Kochiadakis 1998	õ	0	Ő	0	2.2/0	Not estimable		
Cotter 1999	0	4	Ő	4		Not estimable		
Kochiadakis 1999	õ	3	Ő	3		Not estimable		
Redle 1999	õ	2	0	2		Not estimable		
Peuhkurinen 2000	õ	0	Ő	0		Not estimable		
Vardas 2000	0	9	Ő	8		Not estimable		
Kochiadakis 2000	0	119	0	110		Not estimable		
Bianconi 2000	õ	115	0	110		Not estimable		
Elizari 2000	0	271	0	266		Not estimable		
Lee 2000	0	4	0	200		Not estimable		
Maras 2000	0	3	0	3		Not estimable		
Giri 2001	0	3	0	3		Not estimable		
White 2002	0	15	0	13		Not estimable		
Yaqdi 2003	0	6	0	7		Not estimable		
Channer 2004	1	275	0	171	4.1%			
Auer 2004	0	2/5	0	2	4.1%	1.87 [0.08, 45.63]		
	0	48	-	_		Not estimable		
Vora 2004	-		0	48		Not estimable		
Singh 2005	0	734	0	377		Not estimable		
Mitchell 2005	3	12	0	12	5.1%	7.00 [0.40, 122.44]		
Alcalde 2006	0	1	0	1		Not estimable		
Budeus 2006	0	2	0	2		Not estimable		
Zebis 2007	0	10	0	10		Not estimable		
Gu 2009	0	5	0	6		Not estimable		
Balla 2011	0	0	0	0		Not estimable		
Darkner 2012	6	52	0	54	5.1%	13.49 [0.78, 233.59]		
Khitri 2012	0	27	0	41		Not estimable		
Riber 2013	0	10	0	10		Not estimable		
Vilvanathan 2016	0	44	0	45		Not estimable	2016	
Total (95% CI)		5710		5241	100.0%	1.99 [1.04, 3.78]		•
Total events	46		12					
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 7.6$	8, df = 9	0 (P = 0)	$.57$; $I^2 =$	0%		
Test for overall effect:								0.01 0.1 i 10 10

Fig. 5. Skin adverse events. "Total" represents total events per 10,000 person-years. The incident rate of skin adverse events was higher in the amiodarone group versus placebo (81 vs 23; RR: 1.99; 95% CI [1.04–3.78], P = 0.04, I^2 : 0%).

c	Amioda		Place			Risk Ratio		Risk Ratio
Study or Subgroup	Events				Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl
Greco 1989	0	7	0	7		Not estimable		
Hamer 1989	4	8	0	7	1.3%	8.00 [0.51, 126.67]		
Nicklas 1991	0	49	0	52		Not estimable		
Ceremuzynski 1992	0	305	2	308	1.1%	0.20 [0.01, 4.19]		· · · · · · · · · · · · · · · · · · ·
Meyer 1993	0	5	0	5		Not estimable		
Mahmarian 1994	0	8	0	4		Not estimable		
Donovan 1995	0	1	0	1		Not estimable		
Singh 1995	20	1260	16	1268	17.2%	1.26 [0.65, 2.42]		
Galve 1996	0	2	2	2	1.5%	0.20 [0.02, 2.64]		
Gentile 1996	0	12	0	11		Not estimable		
Daoud 1997	1	5	1	5	1.6%	1.00 [0.08, 11.93]		
Julian 1997	22	1300		1300	17.2%	1.47 [0.76, 2.81]		
Cairns 1997	13	1086	8	1068	10.9%	1.60 [0.67, 3.84]		
Kochiadakis 1998	0	0	0	0		Not estimable		
Cotter 1999	0	4	0	4		Not estimable		
Kochiadakis 1999	0	3	0	3		Not estimable		
Redle 1999	2	2	0	2	1.5%	5.00 [0.38, 66.01]	1999	
Bianconi 2000	0	1	0	1		Not estimable	2000	
Elizari 2000	0	271	0	266		Not estimable	2000	
Lee 2000	0	4	0	4		Not estimable	2000	
Peuhkurinen 2000	4	0	2	0		Not estimable	2000	
Vardas 2000	0	9	0	8		Not estimable	2000	
Kochiadakis 2000	0	119	0	110		Not estimable	2000	
Giri 2001	32	3	16	3		Not estimable	2001	
Maras 2001	0	3	0	3		Not estimable	2001	
White 2002	32	15	16	13		Not estimable	2002	
Yagdi 2003	0	6	0	7		Not estimable	2003	
Auer 2004	13	2	13	2		Not estimable	2004	
Vora 2004	0	48	0	48		Not estimable	2004	
Channer 2004	0	275	0	171		Not estimable	2004	
Mitchell 2005	8	12	6	12	15.8%	1.33 [0.67, 2.67]	2005	- -
Singh 2005	0	734	0	377		Not estimable	2005	
Budeus 2006	3	2	0	2		Not estimable	2006	
Alcalde 2006	1	1	1	1	7.1%	1.00 [0.32, 3.10]	2006	
Zebis 2007	0	10	0	10		Not estimable		
Gu 2009	2	5	1	6	2.3%	2.40 [0.30, 19.34]	2009	
Balla 2011	2	0	0	0		Not estimable		
Khitri 2012	7	27	5	41	8.2%	2.13 [0.75, 6.01]		
Darkner 2012	26	52	7	54	14.2%	3.86 [1.84, 8.11]		
Riber 2013	0	10	0	10		Not estimable		
Vilvanathan 2016	0	44	0	45		Not estimable		
Total (95% CI)		5710		5241	100.0%	1.63 [1.18, 2.24]		◆
Total events	192		111					
Heterogeneity: Tau ² = Test for overall effect	= 0.05; Ch		88, df =	12 (P =	= 0.31); I ²	= 14%		0.01 0.1 1 10 1 Placebo Amiodarone

Fig. 6. Gastrointestinal adverse events. "Total" represents total events per 10,000 person-years. The incident rate of gastrointestinal adverse events was higher in patients receiving amiodarone compared to those receiving placebo (336 vs 212; RR: 1.63; 95% CI [1.18–2.24], P = 0.003, l^2 : 14%).

	Amioda	rone	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
Greco 1989	11	7	0	7		Not estimable	1989	
Hamer 1989	1	8	0	7	1.1%	2.67 [0.13, 56.63]	1989	
Nicklas 1991	2	49	0	52	1.1%	5.30 [0.26, 107.70]	1991	
Ceremuzynski 1992	0	305	0	308		Not estimable		
Meyer 1993	0	5	0	5		Not estimable		
Mahmarian 1994	0	8	0	4		Not estimable		
Donovan 1995	0	1	0	1		Not estimable		
Singh 1995	16	1260	6	1268	11.4%	2.68 [1.05, 6.84]		
Galve 1996	0	2	0	2		Not estimable		
Gentile 1996	0	12	0	11		Not estimable		
Daoud 1997	0	5	Ő	5		Not estimable		
Julian 1997	10	1300	8	1300	11.6%	1.25 [0.49, 3.16]		.
Cairns 1997	19	1086	5	1068	10.4%	3.74 [1.40, 9.97]		
Kochiadakis 1998	0	0010	0	0	10.170	Not estimable		
Cotter 1999	0	4	0	4		Not estimable		
Kochiadakis 1999	0	3	0	3		Not estimable		
Redle 1999	0	2	0	2		Not estimable		
Bianconi 2000	0	1	0	1		Not estimable		
Elizari 2000	0	271	0	266		Not estimable		
	0		0			Not estimable		
Lee 2000		4		4				
Peuhkurinen 2000	0	0	2	0		Not estimable		
Vardas 2000	0	9	0	8	1 00/	Not estimable		
Kochiadakis 2000	1	119	0	110	1.0%	2.77 [0.11, 67.41]		
Giri 2001	0	3	0	3		Not estimable		
Maras 2001	0	3	0	3		Not estimable		
White 2002	0	15	0	13		Not estimable		
Yagdi 2003	0	6	0	7		Not estimable		
Auer 2004	0	2	0	2		Not estimable		
Vora 2004	0	48	0	48		Not estimable		
Channer 2004	0	275	0	171		Not estimable		
Singh 2005	0	734	0	377		Not estimable	2005	
Mitchell 2005	0	12	1	12	1.0%	0.33 [0.01, 7.45]	2005	
Budeus 2006	0	2	0	2		Not estimable	2006	
Alcalde 2006	0	1	0	1		Not estimable	2006	
Zebis 2007	0	10	0	10		Not estimable	2007	
Gu 2009	0	5	0	6		Not estimable	2009	
Balla 2011	0	0	0	0		Not estimable	2011	
Khitri 2012	21	27	18	41	62.3%	1.77 [1.19, 2.64]		
Darkner 2012	0	52	0	54		Not estimable		_
Riber 2013	0	10	0	10		Not estimable		
Vilvanathan 2016	0	44	0	45		Not estimable		
Total (95% CI)		5710		5241	100.0%	1.93 [1.41, 2.65]		•
Total events	81		40					
Heterogeneity: Tau ² = Test for overall effect				7 (P = 0	.63); I ² =	0%		
rest for overall effect	03		0001)					Placebo Amiodarone

Fig. 7. Neurological adverse events. "Total" represents total events per 10,000 person-years. The incident rate of neurological adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (140 vs 76; RR: 1.93; 95% CI [1.41–2.65], P < 0.001, 1^2 : 0%).

	Amioda	rone	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
Greco 1989	0	7	0	7		Not estimable	1989	
Hamer 1989	1	8	0	7	13.2%	2.67 [0.13, 56.63]	1989	
Nicklas 1991	0	49	0	52		Not estimable		
Ceremuzynski 1992	9	305	0	308	14.8%	19.19 [1.12, 328.20]		
Meyer 1993	0	5	0	5		Not estimable		
Mahmarian 1994	0	8	0	4		Not estimable		
Donovan 1995	1	1	0	1	17.6%	3.00 [0.24, 37.67]	1995	
Singh 1995	0	1260	0	1268		Not estimable		
Gentile 1996	0	12	0	11		Not estimable		
Galve 1996	0	2	0	2		Not estimable		
Daoud 1997	0	5	0	5		Not estimable		
Julian 1997	5	1300	5	1300	40.1%	1.00 [0.29, 3.45]		
Cairns 1997	5	1086	0	1068	14.4%	10.82 [0.60, 195.40]		
Kochiadakis 1998	Ő	0	õ	0	2	Not estimable		
Cotter 1999	0	4	ő	4		Not estimable		
Kochiadakis 1999	ő	3	ő	3		Not estimable		
Redle 1999	0	2	0	2		Not estimable		
Elizari 2000	0	271	0	266		Not estimable		
Lee 2000	0	4	0	200		Not estimable		
Peuhkurinen 2000	0	0	0	4		Not estimable		
Vardas 2000	0	9	0	8		Not estimable		
	0	119	0	110				
Kochiadakis 2000			-			Not estimable		
Bianconi 2000	0	1	0	1		Not estimable		
Giri 2001	0	3	0	3		Not estimable		
Maras 2001	0	3	0	3		Not estimable		
White 2002	0	15	0	13		Not estimable		
Yagdi 2003	0	6	0	7		Not estimable		
Auer 2004	0	2	0	2		Not estimable		
Vora 2004	0	48	0	48		Not estimable		
Channer 2004	0	275	0	171		Not estimable		
Singh 2005	0	734	0	377		Not estimable		
Mitchell 2005	0	12	0	12		Not estimable		
Budeus 2006	0	2	0	2		Not estimable		
Alcalde 2006	0	1	0	1		Not estimable		
Zebis 2007	0	10	0	10		Not estimable		
Gu 2009	0	5	0	6		Not estimable		
Balla 2011	0	0	0	0		Not estimable		
Khitri 2012	0	27	0	41		Not estimable	2012	
Darkner 2012	0	52	0	54		Not estimable	2012	
Riber 2013	0	10	0	10		Not estimable	2013	
Vilvanathan 2016	0	44	0	45		Not estimable	2016	
Total (95% CI)		5710		5241	100.0%	3.01 [0.87, 10.36]		
Total events	21		5					
Heterogeneity: Tau ² =	0.59; Ch	$i^2 = 5.6$	8, df = 4	(P = 0)	.22); I ² =	30%		0.01 0.1 1 10 100
Test for overall effect:	Z = 1.74	(P = 0.	08)					0.01 0.1 1 10 100 Placebo Amiodarone
								Placebo Amouarone

Fig. 8. Ocular adverse events. "Total" represents total events per 10,000 person-years. The incident rate of ocular adverse events per 10,000 person-years was higher in patients receiving amiodarone versus placebo; however, this never reached statistical significance (37 vs 10; RR: 3.01; 95% CI [0.87–10.36], P = 0.08, I^2 : 30%).

	Amioda	rone	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Greco 1989	3	7	8	7		Not estimable	1989	
Hamer 1989	5	8	0	7	0.5%	9.78 [0.64, 150.51]	1989	· · · · · · · · · · · · · · · · · · ·
Hohnloser 1991	7	0	5	0		Not estimable	1991	
Nicklas 1991	5	49	2	52	1.5%	2.65 [0.54, 13.05]	1991	
Ceremuzynski 1992	55	305	19	308	9.1%	2.92 [1.78, 4.80]		
Meyer 1993	0	5	0	5		Not estimable		
Mahmarian 1994	0	8	0	4		Not estimable		
Donovan 1995	0	1	0	1		Not estimable	1995	
Singh 1995	90	1260	78	1268	14.0%	1.16 [0.87, 1.56]		+-
Galve 1996	0	2	0	2		Not estimable		
Gentile 1996	0	12	0	11		Not estimable		
Daoud 1997	1		1	5	0.7%	1.00 [0.08, 11.93]		
Iulian 1997	214	1300		1300	15.9%	2.14 [1.71, 2.68]		-
Cairns 1997	159	1086	82	1068	15.1%	1.91 [1.48, 2.46]		-
Kochiadakis 1998	1 1	0001	0	0	13.1/0	Not estimable		
Cotter 1999	5	4	0	4		Not estimable		
Kochiadakis 1999	0	3	0	3		Not estimable		
Redle 1999	1	2	2	2	2.4%			
	0	1	2	1	2.4%	0.60 [0.17, 2.07]		
Bianconi 2000	131	271	81		16.0%	Not estimable		+
Elizari 2000				266	16.0%	1.59 [1.27, 1.98]		· · · · · · · · · · · · · · · · · · ·
Lee 2000	2	4	0	4	0.5%	5.00 [0.31, 79.94]		
Peuhkurinen 2000	0	0	0	0		Not estimable		
Vardas 2000	0	9	0	8		Not estimable		
Kochiadakis 2000	15	119	0	110	0.5%	28.68 [1.74, 473.59]		
Giri 2001	10	3	5	3		Not estimable		
Maras 2001	0	3	0	3		Not estimable		
White 2002	9	15	5	13	4.9%	1.56 [0.70, 3.48]		
Yagdi 2003	4	6	2	7	2.2%	2.33 [0.64, 8.57]		
Auer 2004	4	2	5	2		Not estimable		
Vora 2004	3	48	2	48	1.3%	1.50 [0.26, 8.58]		
Channer 2004	11	275	1	171	1.0%	6.84 [0.89, 52.51]	2004	
Mitchell 2005	34	12	16	13		Not estimable	2005	
Budeus 2006	3	2	1	2		Not estimable	2006	
Alcalde 2006	1	1	1	1	2.8%	1.00 [0.32, 3.10]	2006	
Zebis 2007	2	10	1	10	0.8%	2.00 [0.21, 18.69]	2007	
Gu 2009	0	5	1	6	0.5%	0.39 [0.02, 7.88]	2009	
Balla 2011	0	0	0	0		Not estimable	2011	
Khitri 2012	15	27	8	41	5.9%	2.85 [1.40, 5.78]	2012	
Riber 2013	5	10	5	10	4.3%	1.00 [0.42, 2.40]	2013	
Vilvanathan 2016	0	44	0	45		Not estimable	2016	
Total (95% CI)		4924		4811	100.0%	1.79 [1.45, 2.19]		•
Total events	795		431					
Heterogeneity: Tau ² =	0.06; Ch	$i^2 = 33$	12, df =	19 (P =	= 0.02); I ²	= 43%		0.01 0.1 1 10 100
Test for overall effect:	Z = 5.53	(P < 0.	00001)					'0.01 0.1 İ 1'0 100' Placebo Amiodarone
								Flacebo Affilouatone

Fig. 9. Rates of drug discontinuation. "Total" represents total events per 10,000 person-years. The incident rate of drug discontinuation secondary to side effects per 10,000 person-years was higher in the amiodarone group versus placebo (1614 vs 896; RR: 1.79; 95% CI [1.45–2.19], P < 0.001, I^2 : 43%).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dib.2019.104835.

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